Certain Beta-Hpvs Target P300 for Degradation, Likely Disrupting Many Cellular Signaling Pathways

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ME Arnegard

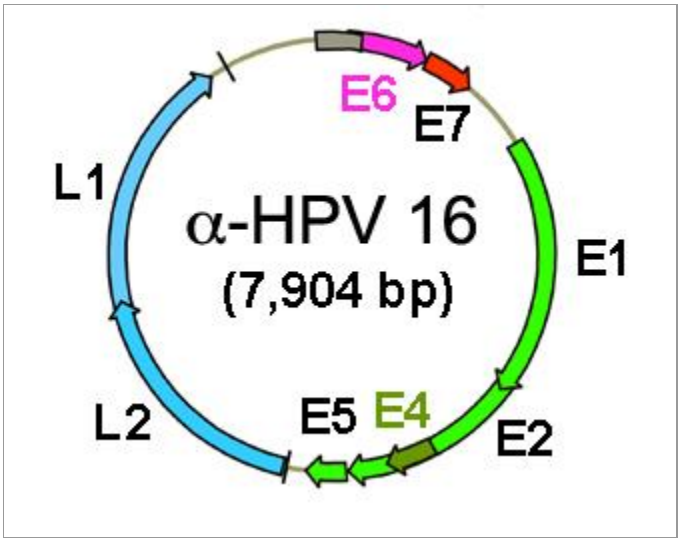
Human beta papillomaviruses (HPVs) make up a large family of viruses that infect keratinocytes, the most common epithelial cell type. HPV infection can cause pathologies ranging from benign papillomas (*e.g.*, common warts) to cancerous lesions. The alpha lineage of HPVs includes low-risk viruses (*e.g.*, HPV types 6 and 11, which account for 90 percent of genital wart cases) and high-risk viruses, which are associated with several anogenital cancers and a subset of head and neck cancers. The most common HPV-induced cancer is cervical cancer, nearly all cases of which are caused by high-risk alpha-HPV infection. Thus, it is no surprise that the alpha lineage has been the focus of most HPV research. However, interest in the beta lineage has increased due to recent evidence linking beta-HPVs to squamous cell skin cancer (SCSC).

The HPV genome comprises genes encoding six early-expressing proteins (E1, E2, E3, E4, E6 and E7) and two late-expressing proteins (L1 and L2). E6 and E7 act as oncoproteins – proteins that are expressed in the viral host and can trigger cancer. E6 and E7 modify the cell cycle of keratinocytes, trapping them in a state favorable for viral genome replication and late gene expression. The functions of E6 and E7 vary among HPV genera and types. For instance, while some E6 functions are conserved among all HPVs from both the alpha and beta lineages, other functions manifest strongly only in high-risk alpha-HPVs. Notably, most beta-HPV E6 proteins cannot directly bind tumor suppressor protein p53, which is a crucial event in carcinogenesis for high-risk alpha-HPVs. A possible role for histone acetyltransferase p300 (a transcriptional coactivator) in SCSC is suggested by its ability to interact with E6 from multiple HPV lineages, as well as its function in a vast number of cellular signaling pathways, including p53 transactivation.

In a recent study from the laboratory of Dr. Denise Galloway (Human Biology Division), Dr. Heather Howie and co-authors aimed to determine which signaling pathways are altered by beta-HPV E6 oncoproteins. They screened lysates of foreskin keratinocytes for proteins that interact with E6 orthologs from beta-HPV types 5, 8 and 38. They did so by genetically engineering constructs of E6 proteins fused to glutathione S-transferase, which has a high affinity for glutathione, allowing ‘pulldown’ of the fusion proteins and the host cell proteins that interact with them. Identities of the

pulled-down proteins were determined by mass spectrometry at the proteomics facility of the Fred Hutchinson Cancer Research Center. Among the hundreds of interaction proteins identified, Howie *et al.* found that E6 from beta-HPV 5 and 8 interact particularly strongly with keratinocyte p300. The team went on to provide experimental evidence that E6 proteins from beta-HPV 5 and 8, but not beta-HPV 38, target p300 for degradation in the proteasome, independent of ubiquitin ligase E6AP, by blocking another cellular protein, AKT, from binding to and stabilizing p300. This results in a lower concentration of p300 in beta-HPV-5 and -8 infected cells compared to normal keratinocytes, an effect that could be reversed by E6 knockdown with siRNA. Lastly, the authors found that decreased p300 levels in cultured cells expressing E6 from beta-HPV 8 attenuated both early and late markers of keratinocyte differentiation. By degrading p300, beta-HPVs 5 and 8 favor their own replication by promoting host-cell proliferation while inhibiting terminal keratinocyte differentiation. This important study further illuminates how certain beta-HPV E6 proteins have the potential to disrupt a number of cellular processes involved in DNA repair, cell growth and differentiation via their interaction with p300. Among the many outcomes of this interaction, degradation of p300 likely attenuates p300-mediated acetylation of p53, suggesting a new route to HPV-induced cancer in the case of SCSC.

Howie HL, Koop JI, Weese J, Robinson K, Wipf G, Kim L, Galloway DA. 2011. Beta-HPV 5 and 8 E6 promote p300 degradation by blocking AKT/p300 association. *PLoS Pathogens* 7:e1002211.



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Human papillomavirus (HPV) genome. Shown here is the 7,904 base pair genome of the high-risk alpha-HPV type 16 virus, used as a control in the present study. Early genes encoding proteins E1 to E7 are indicated in greenish and reddish hues, and late genes encoding proteins L1 and L2 are shown in blue. E6 and E7 are oncoproteins, which play key roles in cervical cancer in the case of alpha-HPV 16. The study by Howie et al. focuses on better understanding the role of beta-HPV E6 (coded by the pink gene) in triggering squamous cell skin carcinoma (SCSC).